REMARKS

Claims 1-17 are pending and under consideration in the instant Application. With the instant amendment, Claims 1, 2, 4, 6, 13 and 16 are canceled without prejudice. Claims 3, 5, 7-8, 10, 12 and 14-15 are amended and new Claims 18-26 are added. Thus, after entry of the instant amendment, Claims 3, 5, 7-12, 14-15 and 17-26 are pending and under consideration. A marked up version of the amended claims is attached hereto as Exhibit B. For the PTO's convenience, a clean copy of claims as pending after entry of this amendment is attached hereto as Exhibit C.

Applicants expressly reserve the right to pursue any canceled subject matter in one or more related, continuation, divisional or continuation-in-part application(s).

I. THE AMENDMENT OF THE SPECIFICATION

The specification has been amended on pages 2 and 6 to correct minor typographical errors. As the amendments to the specification are fully supported by the specification as originally filed, they do not constitute new matter. Entry thereof is therefore respectfully requested.

II. THE AMENDMENT OF THE CLAIMS

Claims 1, 2, 4, 6, 13 and 16 have been canceled without prejudice. Applicants reserve the right to pursue any canceled subject matter in one or more continuation, divisional and/or continuation-in-part applications.

Applicants have amended Claim 3 to recite a method for characterizing an individual as possessing a factor contributing to an increased risk of type 1 diabetes or multiple sclerosis. Support for amended Claim 3 can be found in the specification at, for example, page 38, lines 4-5, page 42, lines 15-17, page 49, lines 17-18 and in Claims 3 and 4, as originally filed. Claim 5 has been amended to recite a method for characterizing an individual as possessing a factor contributing to an increased risk of atopy or allergic asthma. Support for amended Claim 5 can be found in the specification at, for example, page 50, lines 9-10, page 51, lines 8-14 and page 59, 26-28 and in Claims 5 and 6, as originally filed. Claims 7, 8, 10 and 15 have been amended to correct minor formal errors and/or further clarify the claimed subject matter. Amended Claims 7, 8, 10 and 15 are supported by Claims

7, 8, 10 and 15, as originally filed. Claim 12 has been amended to recite an isolated oligonucleotide of about 10 to about 35 nucleotides that is exactly or substantially complementary to SEQ ID NO: 1, or its complement, in a region comprising the polymorphic site at nucleotide position 883, wherein said oligonucleotide is exactly complementary to SEQ ID NO: 1, or its complement, at nucleotide position 883. Support for amended Claim 12 can be found in the specification at, for example, page 5, lines 23-29 and in Claims 12 and 13, as originally filed. Claim 14 has been amended to depend from Claim 12 and is supported by Claim14, as originally filed.

New Claim 18 recites that the TCF-1 gene of Claims 3 or 5 comprises SEQ ID NO: 1. Support for new Claim 18 can be found in the specification, at for example, page 10, lines 13-15 and Claims 1-3 and 5 as originally filed.

New Claim 19 recites a method for determining the presence of an A allele or a C allele of a TCF-1 gene in a sample comprising a nucleic acid, comprising: (a) contacting the nucleic acid with an oligonucleotide exactly complementary to the A allele or the C at position 883 under stringent hybridization conditions; and (b) detecting hybridization wherein, hybridization indicates the presence of said A allele or said C allele. Support for new Claim 19 can be found in the specification at, for example, page 15, lines 23-30 and in Claim 7 as originally filed.

New Claim 20 recites an oligomer fragment that is exactly or substantially complementary to an A allele or a C allele of a TCF-1 gene, or the complements thereof, comprising the nucleotide at position 883, or its complement. New Claim 20 is fully supported in the specification at, for example, page 6, lines 15-20 and 30-31, page 10, lines 13-18 and page 7, lines 24-27. New Claim 21 recites an oligonucleotide of about 10 to about 35 nucleotides that is exactly or substantially complementary to a C allele of a TCF-1 gene, or its complement, comprising the nucleotide at position 883. New Claim 21 is fully supported in the specification at, for example, page 5, lines 23-29, page 6, lines 15-20, page 10, lines 13-18, page 7, lines 24-27 and in Claim 12 as originally filed.

New Claims 22 and 23 recite an isolated oligonucleotide that is exactly or substantially complementary to an A allele at position 883 of a TCF-1 gene. New Claim 22 is fully supported in the specification at, for example, page 6, lines 15-20, page 10, lines 13-18

and page 7, lines 24-27. Support for new Claim 23 can be found in the specification at, for example, page 5, lines 23-29.

New Claims 24-26 recite a method for characterizing an individual as possessing a factor contributing to an increased likelihood of having an increased IgE response. New Claim 24 is fully supported in the specification at, for example, pages 50-60 (entire Example 8). New Claim 25 is fully supported in the specification at, for example, page 10, lines 13-18 and Claims 1-3 and 5 as originally filed. New Claim 26 is fully supported in the specification at, for example, page 50, lines 9-10, page 51, lines 8-14 and page 59, 26-28.

As the amendments to Claims 3, 5, 7-8, 10, 12 and 14 and new Claims 18-26 are fully supported by the specification and claims as originally filed, they do not constitute new matter. Entry thereof is therefore respectfully requested.

III. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-3, 5 and 6 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly being not enabled. Applicants respectfully submit that the cancellation of Claims 1, 2 and 6 renders the rejection of these Claims moot. Applicants respectfully traverse the rejection of Claims 3 and 5.

A claim is enabled if one of skill in the art, guided by Applicant's disclosure, can make and use the claimed invention without undue experimentation. *See Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916); *In re Wands*, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The test is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is not undue. *See In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976). The fact that the required experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985). While Applicants are required to provide an enabling disclosure, the disclosure is not required to teach, "and *preferably omits*, what is well known in the art." *See* M.P.E.P. § 2164.01 (emphasis added); *In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986); *Lindemann Maschinen Fabrik v. American Hoist & Derrick*, 221 USPQ 481, 489 (Fed.

Cir. 1984). Among the factors to be considered when determining whether the necessary experimentation is undue are the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *See In re Wands*, 8 U.S.P.Q.2d at 1404. In rejecting a claim for lack of enablement, the Examiner should cite any of these factors that are relevant, and specific technical reasons are *always required*. *See* M.P.E.P. at §§ 2164.01(a) 2164.04; *In re Wands*, 8 U.S.P.Q.2d at 1404.

Applicants submit that one of skill in the art, guided by the specification, would be fully enabled to practice the full scope of the methods recited in amended Claims 3 and 5.

A. Methods for Characterizing an Individual as Possessing a Factor Contributing to an Increased Risk of Type 1 Diabetes, Multiple Sclerosis, Allergic Asthma or Atopy are Fully Enabled by the Specification

The PTO alleges that methods for characterizing an individual as possessing any factor which leads to an increased tendency for responding to an antigen with a Th1 or Th2 response or for characterizing an individual as possessing a factor contributing to an increased risk of a Th1 or Th2-mediated disease are not enabled by the specification. Although Applicants maintain that Claims 3 and 5, as originally filed, are fully enabled by the specification, Applicants have amended Claims 3 and 5 merely to expedite prosecution and secure rapid allowance of the claims.

Amended Claim 3 recites a method for characterizing an individual as possessing a factor contributing to an increased risk of type 1 diabetes or multiple sclerosis comprising: (a) determining the genotype of said individual with respect to the nucleotide present at position 883 of the TCF-1 gene and (b) classifying said individual based on the result obtained from step (a), wherein the presence of an A allele indicates a factor contributing to an increased risk of type 1 diabetes or multiple sclerosis. Applicants submit that, as acknowledged by the PTO, the specification fully enables methods identifying individuals having an increased likelihood of having multiple sclerosis or type 1 diabetes.

Amended Claim 5 recites a method for characterizing an individual as possessing a factor contributing to an increased risk of atopy or allergic asthma comprising:

(a) determining the genotype of said individual with respect to the nucleotide present at position 883 of the TCF-1 gene and (b) classifying said individual based on the result obtained from step (a), wherein the presence of a C allele indicates a factor contributing to an increased risk of atopy or allergic asthma.

While the PTO acknowledges that the specification enables a method for characterizing an individual as possessing a factor contributing to an increased likelihood of having an increased IgE response, the PTO, citing statements on pages 58 and 59 of the specification, alleges that the specification does not enable a method for diagnosing an increased risk of asthma or atopy. Applicants respectfully submit that asthma is a complex disease with multiple etiologies, one of which is allergic or atopic asthma. *See* page 59, lines 18-25. Amended Claim 5 recites, in part, methods of characterizing an individual as possessing a factor contributing to an increased risk of allergic asthma.

Applicants submit that a method for diagnosing an increased risk of atopy or allergic asthma (atopic asthma), as recited in amended Claim 5, is fully enabled by the specification. As acknowledged by the PTO, the specification teaches a correlation between the level of IgE response and the presence of a C allele at position 883 of the TCF-1 gene. For example, the specification teaches that the data suggest a genetic effect on the level of IgE response. *See* page 57, line 15 through page 58, line 1 and page 58, lines 24-25.

The specification further teaches that the level of IgE response can be used to correlate an increased risk of atopy or allergic asthma to the presence of a C allele at position 883 of the TCF-1 gene. *See, e.g.*, page 59, lines 19-25 of the specification. On page 59, lines 26-28, the specification teaches that "[t]he significant association of the TCF-1 allele with IgE response indicates that genotyping at the TCF-1 locus may provide useful information in characterizing the likelihood of atopic asthma . . . ." Applicants therefore submit that the specification teaches a correlation between a C allele at position 883 of the TCF-1 gene and the level of IgE response and thus a correlation to atopy or allergic asthma and fully enables a method for characterizing an individual as possessing a factor contributing to an increased risk of atopy or allergic asthma.

Applicants submit that the statement on page 58, lines 23-24, that the "data appear to be consistent with an absence of genetic effects contributing to the presence or absence of asthma and atopy" is misleading when taken out of the context of the rest of the disclosure.

In fact a clear association does exist with the secondary measurements of atopic asthma and atopy. The statement cited by the PTO indicates that a direct correlation between the discrete experimental variable asthma and the TCF-1 genotype was not observed in the experiments described in Example 8 of the specification. However, the specification further teaches that "asthma is a poorly defined disease which may have multiple etiologies, including disease not associated with the atopic [or allergic] state," (*see* page 59, lines 18-19 of the specification) and that "[a]lthough asthma is often associated with atopy, asthma is unlikely to be a single disease" (*see* page 50, lines 14-15, of the specification). The limitations of the discrete experimental variable asthma in correlating asthma with TCF-1 genotype "may result from the low number of non-atopic children of heterozygous parents in the study population, *rather than an actual absence of genetic effect.*" *See* page 58, lines 1-4 of the specification (emphasis added). The specification teaches that the methods used to analyze discrete variables such as asthma are more affected by the low number of individuals in the study population than the methods used to analyze continuous variables such as IgE response. *Id.* at lines 4-6. As a result, the methods of Example 8 that evaluate the presence or absence of asthma as a whole (*i.e.*, as a discrete variable) might not unequivocally identify the presence or absence of a clear correlation between an increased risk of atopy or allergic asthma and the presence of a particular TCF-1 allele.

Moreover, as discussed above, Example 8 further demonstrates a correlation between the TCF-1 genotype and the continuous variable of IgE response, and because TCF-1 is part of the pathway affecting IgE production, it is likely that any effect of the TCF-1 allele would be manifest in atopy or allergic asthma. *See* page 59, lines 19-22 of the specification. Analysis of continuous variables, such as IgE response, are better suited to identify a correlation between an increased risk of atopy or allergic asthma and the presence of a particular TCF-1 allele. In fact, the specification teaches that "[t]he methods used to analyze the continuous variables are less affected by the low number of individuals in [the study population] and, thus, are likely to have a greater power to identify a genetic effect." *See* page 58, lines 4-6 of the specification. As discussed above, Example 8 concludes that the correlation between the TCF-1 genotype and IgE response indicates that the TCF-1 genotype can be used to characterize an individual as possessing a factor contributing to an increased risk of atopy or allergic asthma. Accordingly, Applicants submit that the conclusion that the

"data appear to be consistent with an absence of genetic effects contributing to the presence or absence of asthma and atopy," when read in light of the rest of Example 8, indicates the absence of an effect in a small sample of individuals of the TCF-1 genotype on the discrete experimental variable asthma and possibly on asthma as a whole, but not on atopy or allergic asthma. As discussed above, Example 8 demonstrates the correlation of the TCF-1 allele and atopy or allergic asthma.

Therefore, Applicants submit that the specification fully enables a method for characterizing an individual as possessing a factor contributing to an increased risk of allergic asthma or atopy by determining the genotype of the individual with respect to the nucleotide present at position 883 of the TCF-1 gene, as recited in amended Claim 5. Applicants therefore submit that the specification enables one of skill in the art to practice the method claims without undue experimentation.

In view of the foregoing, Applicants respectfully request that the rejection of Claims 1-3, 5 and 6 under 35 U.S.C. § 112, first paragraph, as allegedly being not enabled, be withdrawn.

IV. THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-17 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse the rejection.

A. Amended Claims 3 and 5 are Definite, Clear and do not Lack Proper Antecedent Basis

Claims 1-6 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite and lacking sufficient antecedent basis for the phrase "said gene sequence is provided as SEQ ID NO: 1." Applicants respectfully submit that cancellation of Claims 1, 2, 4 and 6 renders the rejection of these Claims moot. Further, Applicants submit that amended Claims 3 and 5 do not recite the above phrase, rendering the rejection moot. Accordingly, Applicants request that the PTO withdraw its rejection of Claims 1-6 under 35 U.S.C. § 112, second paragraph.

B. Amended Claims 7-11 are Definite and Clear

Claims 7-11 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to recite a final process step which agrees with the preamble. Applicants respectfully submit that amended Claims 7-11 recite a final process step which agrees with the preamble. In addition, the PTO asserts that Claims 8-9 are indefinite because it is unclear as to what each recitation of the word "region" refers to. Applicants submit that amended Claims 8-9 unequivocally define the region of the nucleic acid that is amplified. Further, the PTO asserts that Claims 10-11 are indefinite because it is unclear as to whether the phrase "said allele" refers to the "A allele" or the "C allele." Applicants submit that Claims 10-11 have been amended to replace the phrase "said allele" with the specific alleles and are therefore clear with respect to the allele being referred to in the claims. Applicants therefore submit that amended Claims 7-11 are definite and clear. Accordingly, Applicants request that the PTO withdraw its rejection of Claims 7-11 under 35 U.S.C. § 112, second paragraph.

C. Claims 12, and 15 are not Indefinite

Claims 12, 13, 15 and 16 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting the phrase "substantially complementary." The PTO asserts that the phrase "substantially complementary" is relative and is not clearly defined in the specification. Applicants respectfully submit that the cancellation of Claims 13 and 16 renders the rejection of these Claims moot.

With respect to Claims 12 and 15, Applicants submit that under 35 U.S. C. § 112, second paragraph, the "specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." The "claims must have a clear and definite meaning when construed in light of the *complete patent document*." *Standard Oil Co. v. American Cyanamid Co.*, 227 USPQ 293, 296 (Fed. Cir. 1985) (emphasis added). If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more." *Personalized Media Communications, LLC v. U.S. Int'l Trade Comm'n*, 48 USPQ2d 1880, 1888 (Fed. Cir. 1998); *see also Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994).

Applicants respectfully submit that "substantially complementary" is defined in the specification at, for example, page 7, lines 24-27. The specification states that "substantially complementary" refers to sequences that are complementary except for minor regions of mismatch. In fact, the specification goes even further and *quantitates* the term by stating that "the total number of mismatched nucleotides is no more than about 3 for sequences about 15 to about 35 nucleotides in length." Applicants therefore submit that the level of complementarity encompassed by the phrase "substantially complementary," when read in light of the specification, would reasonably apprise those skilled in the art of the scope of the invention. Therefore, Claims 12 and 15 have a clear and definite meaning when construed in light of the complete patent document. Applicants therefore request that the PTO withdraw its rejection of Claims 12, 13, 15 and 16 under 35 U.S.C. § 112, second paragraph.

D. Claims 12, 14, 15 and 17 are Definite and Clear

Claims 12-17 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting "either strand of SEQ ID NO: 1." Applicants respectfully submit that the cancellation of Claims 13 and 16 renders the rejection of these Claims moot. Further, Applicants submit that amended Claims 12, 14, 15 and 17 do not recite the above phrase, rendering the rejection moot. Applicants therefore submit that amended Claims 12-17 are definite and clear. Accordingly, Applicants request that the PTO withdraw its rejection of Claims 12-17 under 35 U.S.C. § 112, second paragraph.

In view of Sections A-D above, Applicants respectfully request that the rejection of Claims 1-17 under 35 U.S.C. § 112, second paragraph, be withdrawn.

V. REJECTION UNDER 35 U.S.C. § 102

Claims 12 and 13 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by van de Wetering *et al.*, 1992, *J. Biol. Chem.* 267:8530-8536 ("van de Wetering"). Applicants respectfully traverse the rejection of Claim 12. Applicants respectfully submit that the cancellation of Claim 13 renders the rejection of this Claim moot.

The standard for anticipation under 35 U.S.C. §102 is strict identity. Anticipation under §102 can only be established by a single prior art reference that teaches each and every

element of the claimed invention. *Structural Rubber Products Co. v. Park Rubber Co.* 223 USPQ 1264 (1984).

Amended Claim 12 recites, *inter alia*, an isolated oligonucleotide of about 10 to about 35 nucleotides that is exactly or substantially complementary to SEQ ID NO: 1, or its complement, in a region which encompasses the polymorphic site at nucleotide position 883, and wherein the oligonucleotide is exactly complementary to SEQ ID NO: 1, or its complement, at nucleotide position 883.

van de Wetering teaches the full length TCF-1 gene, including both exons and introns. van de Wetering does not teach or suggest an isolated oligonucleotide of about 10 to about 35 nucleotides encompassing the polymorphic site at nucleotide position 883, wherein the oligonucleotide is exactly complementary to SEQ ID NO: 1, or its complement, at nucleotide position 883. In fact, van de Wetering does not teach or suggest any isolated oligonucleotide of about 10 to about 35 nucleotides, nor does it teach or suggest any importance of the polymorphic site at nucleotide position 883.

Since van de Wetering does not teach or suggest an isolated oligonucleotide of about 10 to about 35 nucleotides encompassing the polymorphic site at nucleotide position 883, wherein the oligonucleotide is exactly complementary to SEQ ID NO: 1, or its complement, at nucleotide position 883, it does not anticipate amended Claim 12. Applicants respectfully request that the rejection of Claims 12 and 13 under 35 U.S.C. § 102 be withdrawn.

VI. THE REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 15 and 16 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over van de Wetering. Applicants respectfully traverse the rejection of Claim 15. Applicants respectfully submit that the cancellation of Claim 16 renders the rejection of this Claim moot.

A. The Legal Standard of *Prima Facie* Obviousness

To reject claims in an application under 35 U.S.C. § 103, the PTO bears the initial burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); MPEP § 2142. In the absence of establishing a proper *prima facie* case of obviousness, applicants who comply with the other statutory requirements are entitled to a

patent. *In re Oetiker*, 24 USPQ2d. 1443, 1444 (Fed. Cir. 1992). In order to establish *prima facie* obviousness, three basic criteria must be met.

First, the prior art must provide one of ordinary skill in the art with a suggestion or motivation to modify or combine the teachings of the references relied upon by the PTO to arrive at the claimed invention. When an obviousness determination relies on one reference, there must be suggestion or motivation to modify the teaching of the reference in the manner suggested by the PTO. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). Alternatively, when an obviousness determination relies on a combination of two or more references, there must be some suggestion or motivation to combine the references. *WMS Gaming Inc. v. International Game Technology*, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). The suggestion or motivation to combine the references may arise in the references themselves, from the knowledge of those of ordinary skill in the art or may be inferred from the nature of the problem. *See id.* The mere fact that references *could* be modified or combined does not render the resultant modification or combination obvious unless the prior art also suggests the desirability of the modification or combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP § 2143.01. In addition, if a proposed modification would render the prior art unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984); MPEP § 2143.01.

Second, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success. Thus, the skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the PTO would succeed. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

Third, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. *In re Royka* 180 USPQ 580 (C.C.P.A. 1974); *In re Wilson* 165 USPQ 494 (C.C.P.A. 1970); MPEP § 706.02(j). The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicants' disclosure. *In re Vaeck* 20 USPQ2d 1438 (Fed. Cir. 1991). If any one of these criteria are not met, *prima facie* obviousness is not established. Further, if the prior art provides no motivation or incentive to make the claimed invention, then Applicants are *not* required to show new or unanticipated results since *prima facie* obviousness has not been established. *In re Grabiak* 226 USPQ 870 (Fed. Cir. 1985).

B. Claims 15 and 16 are not Obvious Over van de Wetering

As discussed in Section A above, in order to establish *prima facie* obviousness, the PTO must cite a suggestion or motivation in the art to modify the reference to arrive at Applicants' invention. Applicants submit that the cancellation of Claim 16 renders the rejection of this Claim moot. Further, Applicants respectfully submit that the PTO has failed to meet the burden of demonstrating motivation to modify the teachings of van de Wetering, thereby failing to establish *prima facie* obviousness against Claim 15.

Claim 15 recites a kit for determining the genotype of an individual with respect to the nucleotide present in the TCF-1 gene at position 883 comprising an isolated oligonucleotide of about 10 to about 35 nucleotides that is exactly or substantially complementary to SEQ ID NO: 1, or its complement, in a region which encompasses the polymorphic site at nucleotide position 883. The oligonucleotide is exactly complementary to SEQ ID NO: 1, or its complement, at nucleotide position 883.

As acknowledged by the PTO, van de Wetering does not teach kits. The PTO, however, alleges that it would have been obvious, based on the teachings of van de Wetering, to one of skill in the art to have packaged the TCF-1 gene in a kit. van de Wetering teaches the structure of the full length TCF-1 gene, including both exons and introns. However, as discussed above, van de Wetering does not teach or suggest an isolated oligonucleotide of about 10 to about 35 nucleotides encompassing the polymorphic site at nucleotide position 883, wherein the oligonucleotide is exactly complementary to SEQ ID NO: 1, or its complement, at nucleotide position 883.

Further, van de Wetering does not teach or suggest the importance of the nucleotide at position 883. Applicants therefore submit that, based on the teachings of van de Wetering, one of skill in the art would have had no motivation to target position 883 and to package an isolated oligonucleotide of about 10 to about 35 nucleotides of SEQ ID NO: 1 that comprises the polymorphic site at nucleotide position 883.

Since van de Wetering neither teaches nor suggests a kit for determining the genotype of an individual TCF-1 genotype with respect to the nucleotide present in the TCF-1 gene at position 883 comprising an isolated oligonucleotide of about 10 to about 35 nucleotides that is exactly or substantially complementary to SEQ ID NO: 1, or its complement, in a region which encompasses the polymorphic site at nucleotide position 883, the PTO's references

fails to teach or suggest each and every element of Claim 15. The reference is therefore not sufficient to establish a *prima facie* case of obviousness against Claim 15.

In view of the foregoing, Applicants respectfully request that the rejection of Claims 15 and 16 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants submit that Claims 3, 5, 7-12, 14-15 and 17-26 satisfy all the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 3, 5, 7-12, 14-15 and 17-26 to issuance is therefore kindly solicited.

No fee is believed due with this Amendment. However, pursuant to 37 CFR § 1.136(a)(3), the Commissioner is authorized to charge all required fees, fees under 37 CFR § 1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds, LLP U.S. Deposit Account No. 16-1150 (order no. 1803-300-999).

Respectfully submitted,

Date: December 11, 2002

42,983
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EXHIBIT A

MARKED UP VERSION OF AMENDED PARAGRAPHS

On page 2, line 25, please replace the paragraph beginning "Genetically determined differences . . ." with the following:

Genetically determined differences in T-cell differentiation may determine the nature of the T cell response to an antigen, and thus whether there are pathogenic or non-pathogenic consequences. Although the control of T cell differentiation remains to be elucidated, many components of the cascade-like system of genes that control T cell differentiation have been identified. T cell-specific transcription factor TCF-1 (now officially referred to as TCF-7) is one component of the system of genes that control T cell differentiation. The TCF-1 gene has been cloned and the sequence and structure have been described (see van der Wetering et al., 1992, J. Biol. Chem. [367] 267 (12):8530-8536; van der Wetering et al., 1996, Molecular and Cellular Biology 16(3):745-[7852] 752; both incorporated herein by reference).

On page 6, please replace the paragraph beginning "The term "TCF-1 gene" refers to . . ." with the following:

The term "TCF-1 gene" refers to the genomic nucleic acid sequence that encodes the T cell-specific transcription factor protein, specifically, the gene sequence available from GenBank under accession number X63901 and shown in [Figure] Table 1, and allelic variants thereof. The nucleotide sequence of the gene, as used herein, encompasses both coding regions, referred to as exons, and intervening, non-coding regions, referred to as introns.

On page 6, please replace the paragraph beginning "As used herein, a "C allele" refers to . . ." with the following:

As used herein, a "C allele" refers to a nucleotide sequence variant of the gene. As used herein, a "C allele" refers to sequence variants that contain a cytosine at the polymorphic position which is nucleotide position 883 of the TCF-1 gene strand shown in [Figure] Table 1. As used herein, an "A allele" refers to sequence variants that contain an adenosine at nucleotide position 883 of the TCF-1 gene strand shown in [Figure] Table 1. It will be clear that in a double stranded form, the complementary strand of each allele will contain the complementary base at the polymorphic position.

EXHIBIT B

MARKED UP VERSION OF AMENDED CLAIMS

3. (Amended) A method for characterizing an individual as possessing a factor contributing to an increased risk of [a Th1-mediated disease, wherein said method comprises] type 1 diabetes or multiple sclerosis comprising:

(a) determining the genotype of said individual with respect to the nucleotide present at position 883 of the TCF-1 gene[, wherein said gene sequence is provided as SEQ ID NO: 1];

(b) classifying said [patient] individual based on the result obtained from step (a), wherein the presence of an A allele indicates a factor contributing to an increased risk of [a Th1-mediated disease] type 1 diabetes or multiple sclerosis.

5. (Amended) A method for characterizing an individual as possessing a factor contributing to an increased risk of [a Th2-mediated disease, wherein said method comprises] atopy or allergic asthma comprising:

(a) determining the genotype of said individual with respect to the nucleotide present at position 883 of the TCF-1 gene[, wherein said gene sequence is provided as SEQ ID NO: 1];

(b) classifying said [patient] individual based on the result obtained from step (a), wherein the presence of a C allele indicates a factor contributing to an increased risk of [a Th2-mediated disease] atopy or allergic asthma.

7. (Amended) A method for determining the genotype of a sample comprising a nucleic acid with respect to the nucleotide present in [the] a TCF-1 gene at position 883, comprising:

(a) contacting the nucleic acid [from said sample] with an oligonucleotide probe exactly complementary to [an allele that is] an A allele or a C allele in a region encompassing position 883 under conditions such that hybridization occurs if and only if [said allele] the A allele or the C allele is present; and

(b) detecting if hybridization occurs, [which indicates the presence of said allele] wherein, hybridization to the A allele indicates that the genotype of the sample corresponds to the A allele and hybridization to the C allele indicates that the genotype of the sample corresponds to the C allele.

8. (Amended) [A] The method of Claim 7, wherein [a segment of region of said nucleic acid] the region encompassing [said region] position 883 is amplified prior to, or concurrent with step (a).

10. (Amended) A method for determining the genotype of a sample comprising a nucleic acid with respect to the nucleotide present in [the] a TCF-1 gene at position 883, comprising:

(a) contacting the nucleic acid [from said sample] with [a set of oligonucleotide primers comprising an allele-specific primer specific for an allele that is] one or more allele-specific primers specific for an A allele or a C allele under amplification conditions such that amplification occurs using said allele-specific primer if and only if [said allele] the A allele or the C allele is present; and

(b) detecting if amplifications occurs, [which indicates the presence of said allele] wherein, amplification of the A allele indicates that the genotype of the sample corresponds to the A allele and amplification of the C allele indicates that the genotype of the sample corresponds to the C allele.

12. (Amended) An isolated oligonucleotide of about 10 to about 35 nucleotides, wherein said oligonucleotide is exactly or substantially complementary to [either strand of] SEQ ID NO: 1 or its complement in a region which encompasses the polymorphic site at nucleotide position 883, and wherein said oligonucleotide is exactly complementary to SEQ ID NO: 1 or its complement at said nucleotide position 883.

14. (Amended) [An] The isolated oligonucleotide of Claim [13] 12 selected from the group consisting of GZ351B (SEQ ID NO: 4), GZ374B (SEQ ID NO: 5), KW196 (SEQ ID NO: 8), KW118 (SEQ ID NO: 9), and [the exact] complements thereof.

15. (Amended) A kit for determining the genotype of an individual [TCF-1 genotype] with respect to the nucleotide present in the TCF-1 gene at position 883 locus comprising an oligonucleotide of Claim 12.

EXHIBIT C

PENDING CLAIMS AFTER ENTRY OF INSTANT AMENDMENT

3. (Amended) A method for characterizing an individual as possessing a factor contributing to an increased risk of type 1 diabetes or multiple sclerosis comprising:

(a) determining the genotype of said individual with respect to the nucleotide present at position 883 of the TCF-1 gene;

(b) classifying said individual based on the result obtained from step (a), wherein the presence of an A allele indicates a factor contributing to an increased risk of type 1 diabetes or multiple sclerosis.

5. (Amended) A method for characterizing an individual as possessing a factor contributing to an increased risk of atopy or allergic asthma comprising:

(a) determining the genotype of said individual with respect to the nucleotide present at position 883 of the TCF-1 gene;

(b) classifying said individual based on the result obtained from step (a), wherein the presence of a C allele indicates a factor contributing to an increased risk of atopy or allergic asthma.

7. (Amended) A method for determining the genotype of a sample comprising a nucleic acid with respect to the nucleotide present in a TCF-1 gene at position 883, comprising:

(a) contacting the nucleic acid with an oligonucleotide probe exactly complementary to an A allele or a C allele in a region encompassing position 883 under conditions such that hybridization occurs if and only if the A allele or the C allele is present; and

(b) detecting if hybridization occurs, wherein, hybridization to the A allele indicates that the genotype of the sample corresponds to the A allele and hybridization to the C allele indicates that the genotype of the sample corresponds to the C allele.

8. (Amended) The method of Claim 7, wherein the region encompassing position 883 is amplified prior to, or concurrent with step (a).

9. A method of Claim 8, wherein said probe is selected from the group consisting of KW196 (SEQ ID NO: 8) or KW118 (SEQ ID NO: 9).

10. (Amended) A method for determining the genotype of a sample comprising a nucleic acid with respect to the nucleotide present in a TCF-1 gene at position 883, comprising:

(a) contacting the nucleic acid with one or more allele-specific primers specific for an A allele or a C allele under amplification conditions such that amplification occurs using said allele-specific primer if and only if the A allele or the C allele is present; and

(b) detecting if amplifications occurs, wherein, amplification of the A allele indicates that the genotype of the sample corresponds to the A allele and amplification of the C allele indicates that the genotype of the sample corresponds to the C allele.

11. A method of Claim 10, wherein said allele specific primer is GZ351B (SEQ ID NO: 4) or GZ374B (SEQ ID NO: 5).

12. (Amended) An isolated oligonucleotide of about 10 to about 35 nucleotides, wherein said oligonucleotide is exactly or substantially complementary to SEQ ID NO: 1, or its complement, in a region which encompasses the polymorphic site at nucleotide position 883, and wherein said oligonucleotide is exactly complementary to SEQ ID NO: 1, or its complement, at said nucleotide position 883.

14. (Amended) The isolated oligonucleotide of Claim 12 selected from the group consisting of GZ351B (SEQ ID NO: 4), GZ374B (SEQ ID NO: 5), KW196 (SEQ ID NO: 8), KW118 (SEQ ID NO: 9), and complements thereof.

15. (Amended) A kit for determining the genotype of an individual with respect to the nucleotide present in the TCF-1 gene at position 883 locus comprising an oligonucleotide of Claim 12.

17. A kit for determining the genotype of an individual TCF-1 genotype with respect to the nucleotide present in the TCF-1 gene at position 883 locus comprising an oligonucleotide of Claim 14.

18. (New) The method of claim 3 or 5, wherein said TCF-1 gene comprises SEQ ID NO: 1, an A allele of SEQ ID NO: 1 or the complements thereof.

19. (New) A method for determining the presence of an A allele or a C allele of a TCF-1 gene in a sample comprising a nucleic acid, comprising:

(a) contacting the nucleic acid with an oligonucleotide exactly complementary to the A allele or the C at position 883 under stringent hybridization conditions; and

(b) detecting hybridization wherein, hybridization to the A allele indicates the presence of the A allele and hybridization to the C allele indicates the presence of the C allele.

20. (New) An oligomer fragment of an A allele or a C allele of a TCF-1 gene or the complements thereof, wherein the oligomer fragment comprises the nucleotide at position 883, or its complement.

21. (New) An oligonucleotide of about 10 to about 35 nucleotides that is exactly or substantially complementary to a C allele of a TCF-1 gene, or its complement, wherein the oligonucleotide comprises the nucleotide at position 883, or its complement.

22. (New) An oligonucleotide that is exactly or substantially complementary to an A allele of a TCF-1 gene, or its complement, wherein the oligonucleotide comprises the nucleotide at position 883, or its complement.

23. (New) The oligonucleotide of Claim 22 wherein the oligonucleotide is about 10 to about 35 nucleotides in length.

24. (New) A method for characterizing an individual as possessing a factor contributing to an increased likelihood of having an increased IgE response comprising:

(a) determining the genotype of said individual with respect to the nucleotide present at position 883 of the TCF-1 gene;

(b) classifying said individual based on the result obtained from step (a), wherein the presence of a C allele indicates a factor contributing to an increased likelihood of having an increased IgE response.

25. (New) The method of claim 24, wherein said TCF-1 gene comprises SEQ ID NO: 1, an A allele of SEQ ID NO: 1 or the complements thereof.

26. (New) The method of claim 24, wherein said increased IgE response is associated with atopy or allergic asthma.